

# BRIEF COMMUNICATION

## Hereditary Retinoblastoma and Risk of Lung Cancer

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Patients who have survived hereditary retinoblastoma are at increased risk of dying of a sarcoma, a melanoma, or a brain tumor. The increased risk has been attributed to germline mutations in the retinoblastoma-1 (RB1) gene, which encodes the cell cycle regulatory protein pRb (1). However, the extent to which patients with hereditary retinoblastoma are at increased risk of dying of common epithelial cancers of adulthood, such as lung cancer, is unknown. Somatic mutations in the RB1 gene are known to contribute to the development of lung cancer (2,3), and evidence of increased risk of lung cancer in adult RB1 mutation carriers has been reported (4,5), but questions remain about the association between hereditary retinoblastoma and lung cancer risk (6). In our earlier follow-up studies of 1604 one-year survivors of retinoblastoma (1,7) followed for a median of 17 years, we did not detect an increased risk of lung cancer, but few patients had reached 40 years of age, when the incidence rates for most epithelial cancers begin to rise. After 7 additional years of follow-up, we have again assessed these patients' risk of dying of lung cancer.

The cohort consists of 964 patients with hereditary retinoblastoma (60%) and 640 patients with nonhereditary retinoblastoma (40%) who were followed from 1 year after retinoblastoma diagnosis in 1914 through 1984 (Table 1). Patients with bilateral tumors or unilateral tumors with a family history of retinoblastoma were classified as having hereditary retinoblastoma. The earlier mortality study (1) was based on follow-up from 1925 through 1990.

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**Table 1.** Selected characteristics of 1604 one-year survivors of retinoblastoma

Characteristic	Hereditary retinoblastoma patients (%)	Nonhereditary retinoblastoma patients (%)	Total (%)
No. of subjects	964 (100)	640 (100)	1604 (100)
Sex			
Male	513 (53.2)	334 (52.2)	847 (52.8)
Female	451 (46.8)	306 (47.8)	757 (47.2)
Age at last follow-up, y			
<40	825 (85.6)	515 (80.5)	1340 (83.5)
≥40	139 (14.4)	125 (19.5)	264 (16.5)
Vital status			
Alive	604 (62.7)	519 (81.1)	1123 (70.0)
Lost to follow-up	51 (5.3)	49 (7.7)	100 (6.2)
Deaths	309 (32.1)	72 (11.3)	381 (23.8)
Cancer deaths*	129 (41.7)†	10 (13.9)†	139 (36.5)†

\*Nonretinoblastoma cancer deaths.

†Percent of all deaths.

(Bethesda, MD) approved this study, in which we linked the cohort with the National Death Index Plus to ascertain new deaths and causes of these deaths through December 31, 1997. Among the patients with hereditary retinoblastoma, 71 females and 68 males had survived to 40 years of age or more by the end of 1997. The standardized mortality ratio (SMR) for the period from 1925 through 1997 was calculated as the ratio of the observed number of deaths among the retinoblastoma patients to the expected number of deaths estimated from the appropriate U.S. age-, sex-, and calendar-year cause-specific death rates (8). Exact 95% confidence intervals (CIs) were computed, assuming that the number of deaths followed a Poisson distribution.

After 7 additional years of follow-up, the risk of death from cancers other than retinoblastoma was higher for patients with hereditary retinoblastoma (observed = 129; expected = 2.75; SMR = 47 [95% CI = 39–56]) than for patients with nonhereditary retinoblastoma (observed = 10; expected = 2.63; SMR = 3.8 [95% CI = 1.8–7.0]) (Table 1). During the 7 additional years of follow-up, there were 50 new deaths in the entire cohort attributable to tumors other than retinoblastoma, predominantly cancers of the bone (13 cases), connective tissue (12 cases), and lung (five cases).

Although one case of lung cancer had been reported previously in this cohort (1), subsequent examination of medical records indicates that this cancer, observed in a 12-year-old boy, was probably a metastatic osteosarcoma; therefore, it was excluded from our analyses.

There was a statistically significantly elevated risk of death from lung cancer among patients with hereditary retinoblastoma (observed = 5; expected = 0.33; SMR = 15.2 [95% CI = 4.9–35]). It is interesting that two lung cancer deaths occurred in patients who received radiotherapy (SMR = 8.1 [95% CI = 1.0–29]) and three occurred in patients who did not (SMR = 35 [95% CI = 7.0–102]), because radiotherapy has been linked with lung cancer in other populations. No lung cancer deaths occurred among patients with nonhereditary retinoblastoma. Histology was available for four of the five lung cancers from the patients with hereditary retinoblastoma (Table 2). Two cancers were small-cell lung carcinomas, one cancer was a mixed small-cell/large-cell carcinoma, and one cancer was an adenocarcinoma.

Several case series and case reports have provided suggestive evidence that lung cancer risk is increased in patients with hereditary retinoblastoma. A case

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**Table 2.** Characteristics of lung cancer deaths in a cohort of 1-year survivors of retinoblastoma

Sex	Laterality	Radiotherapy	Lung cancer histology	Age at death, y	Smoking history	Comments
Female	Bilateral	Yes	Unknown	39	60-pack-year smoker	Father, paternal grandfather, and uncle died of lung cancer.
Female	Bilateral	No	Mixed small-cell/large-cell carcinoma	40	19-pack-year smoker	
Female	Bilateral	Yes	Small-cell carcinoma	40	20-pack-year smoker	Patient was also diagnosed with basal cell carcinoma of the eyelid.
Female	Bilateral	No	Adenocarcinoma	52	Never smoked	Both parents smoked; mother died of lung cancer.
Female	Bilateral	No	Small-cell carcinoma	64	Modest smoker for many years	Patient was also diagnosed with malignant melanoma, basal cell carcinoma of the lip, and leiomyosarcoma of the uterus.

report in 1972 (9) described a small-cell lung cancer in a 45-year-old male who had bilateral retinoblastoma. Among 27 adults who survived retinoblastoma from the Manchester Children's Tumour Registry, there were nine cancer deaths, including four lung cancer deaths in men at the ages of 47, 52, 54, and 56 years (4). Additional case reports noted small-cell lung cancers in a 55-year-old male patient with hereditary retinoblastoma (10) and in a 28-year-old male patient with hereditary retinoblastoma who smoked cigarettes (11).

In addition, in a cohort of 4101 parents, grandparents, aunts, and uncles of British retinoblastoma patients that included 117 RB1 mutation carriers (retinoblastoma survivors or unaffected carriers), the lung cancer SMR for these RB1 mutation carriers was 15.4 (95% CI = 6.6–30) based on eight lung cancer deaths (in four bilateral and two unilateral retinoblastoma survivors and in two unaffected carriers) (5). Including two lung cancer deaths in women that occurred after the study ended, a total of 10 lung cancers were reported in the RB1 mutation carriers (six males and four females; 34 through 62 years of age at diagnosis; six small-cell carcinomas, one adenocarcinoma, and three cancers of unknown histology) (5).

In contrast to these reports, several studies (12–17) have reported no lung cancers in cohorts of retinoblastoma survivors; however, these cohorts have been small or have had few patients followed beyond early adulthood. Studies of relatives of retinoblastoma patients (18–26) have yielded mixed results with respect to non-ocular cancers, with one study (22) suggesting that increased risk of such cancers in retinoblastoma families is due to genetic predisposition independent of RB1 mutations.

Overall, our results, together with earlier reports (4,5), establish that germline RB1 mutations confer an increased risk of lung cancer. The preponderance of males among the previously reported lung cancers in RB1 mutation carriers (i.e., 13 men and four women) suggests that our female excess is a chance occurrence. The relative excess of male lung cancers in the earlier reports [i.e., (4,5,9–11)] probably reflects the much higher smoking rates in men than in women in earlier time periods.

Four of the five women who developed lung cancer during the extended follow-up were cigarette smokers, and the fifth had parents who smoked cigarettes from her birth until she left home; she developed adenocarcinoma, the most frequently observed histologic type of lung cancer in women (27). Small-cell carcinomas are more likely to have somatic mutations or deletions in RB1 (2,28,29), and there was a predominance of small-cell lung histology among the lung cancer patients in our study who smoked (Table 2). Among the 17 RB1 mutation carriers reported previously to have developed lung cancer, smoking information was given for only one patient who was a smoker (11). Histology was reported for 10 patients, and small-cell carcinomas predominated [nine small-cell carcinomas and one adenocarcinoma (5,9–11)], which suggests that the patients may have been smokers.

Lung cancer was diagnosed by 40 years of age in the three heaviest smokers in our study (Table 2). In an earlier study, lung cancer diagnosed before 55 years of age was reported in five first-degree relatives of retinoblastoma patients, and four of these relatives were cigarette smokers (24). The first 610 completed interviews from an ongoing

survey of the retinoblastoma survivors in our study indicate that 45% of the patients with nonhereditary retinoblastoma and 33% of the patients with hereditary retinoblastoma had ever smoked cigarettes and that 24% of the patients with nonhereditary retinoblastoma and 17% of the patients with hereditary retinoblastoma were smoking at last contact, with similar percentages for patients with bilateral and unilateral hereditary retinoblastomas. These smoking rates, which are similar to those of the general population, are surprising in a group that should receive intense medical surveillance. Because smoking rates are not abnormally high in retinoblastoma survivors and no lung cancer deaths were reported for the patients with nonhereditary retinoblastoma, our reported excess of early-onset lung cancers suggests that carriers of RB1 mutations may be highly susceptible to smoking-induced lung cancers. If so, patients with hereditary retinoblastoma should be specially targeted for smoking cessation (30).

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## NOTES

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